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Powering Brain Power: GLUT1 and the Era of Structure Based Human Transporter Biology

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Every student of biochemistry quickly appreciates the central role of glycolysis in cellular metabolism. What is not usually addressed in an introductory course is how glucose gets inside a cell in the first place. Specialized integral membrane proteins known as transporters are responsible for glucose uptake; in mammals, glucose is imported by members of the GLUT family of which 14 different varieties have been identified in humans (2). GLUT transporters are members of the Major Facilitator Superfamily of transporters and catalyze the facilitated uptake of glucose in the thermodynamically favored direction. The most widely distributed version is GLUT1 that is responsible for getting glucose into red blood cells and across the blood brain barrier, among many other roles (3).

As a relatively abundant membrane protein (comprising ∼15% of the membrane proteins in red blood cells), GLUT1 has been the subject of many pioneering transport studies, including the key contribution of Widdas (4) that glucose transport is mediated by a carrier that can alternately access the two sides of the membrane. An essential role for GLUT1 is keeping brains cells fueled with glucose; as the brain operates at ∼20 watts (5), this metabolic engine consumes over 10^{18} molecules of glucose per second. To satisfy this demand, the brain needs a minimum of 10^{15} GLUT1 transporters operating at their maximal speed ($\sim 10^3$ s^{-1}). In view of the consequences of perturbing the cellular energy supply, it is not surprising that mutations in GLUT1 and other GLUT family members are associated with various diseases, or that cancer cells requiring more glucose have increased levels of this transporter to fuel their malignant metabolism.

Given the essential physiological roles, the recent crystal structure determination of GLUT1 by Nieng Yan and coworkers (1) represents a landmark accomplishment, by providing an atomic resolution foundation to understand the function of this remarkable protein at the molecular level. GLUT1 is the first structurally characterized human transporter of known substrate, and together with ABCB 10 (6), one of only two structurally characterized human transporters. From the structure, a mechanistic model for GLUT1 transport was developed that provides a framework for understanding the disease consequences of GLUT1 mutants. Beyond the biological impact, the structure determination not only gets high scores for artistic quality, but also represents a significant degree of technical difficulty; success was not the result of luck but rather required inspired experimental design and hard work.

What's next? With the structure of the inward facing conformation solved, the next challenge will be to trap and structurally characterize GLUT1 in other mechanistically relevant states (outward facing, occluded) and in the presence of substrates. Although

GLUT1 is a uniporter, the transport kinetics are non-trivial and beg a molecular interpretation (3). Building on this knowledge, therapeutics may be developed to regulate the function of GLUT1 in response to mutation and cancer. Realizing these long-term goals will require a significant amount of glucose-fueled brain power, but the crucial first step has been brilliantly taken by Yan and coworkers.

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Highlighting

Deng D, Xu C, Sun PC, Wu JP, Yan CY, Hu MX, Yan N. Crystal structure of the human glucose transporter GLUT1. *Nature* **510**, 121-125 (2014).